REMARKS

Re: Rejections under 35 USC 112 (first paragraph):
Claim 1 is amended to require the human Interleukin-2 variant to be the N88R variant of the examples and the N88R acronym is spelled out in its first use in the claims. Basis for the language of the amendment can be found in the first paragraph under the heading SPECIFIC EMBODIMENTS at page 5. The wording to amend claim 1 is taken almost verbatim from the second sentence of that paragraph.

Re: Rejections under 35 USC 112 (second paragraph):
Although it was not clear how the use of "including" in claims 4, 5 and 6 conflict with the guidelines of MPEP 2173.05(d) that word has been replaced with --comprising-- in an earnest effort to address the rejection of those claims under 35 USC 112 (second paragraph) on the ground "including" is vague and indefinite.

Re: Rejections under 35 USC 103 (a): Applicants request reconsideration of claims 1-6 in view of Hora et al. in view of Lee under 35 USC 103 (a). Although Hora et al. list amino acids as stabilizers it is known that not all amino acids stabilize proteins. For example, Taneja and Ahmad (1994), copy enclosed, evaluated the effect of amino acids on the stability of cytochrome c. A total of 13 amino acids were tested, and histidine was found to destabilize the protein both in terms of protein transition temperature (T_m) and free energy of stabilization (ΔG). It was believed that histidine might behave as a protein denaturant because part of the structure is similar to that of urea, a commonly used denaturant.

In a different report, Rishi et al. (1998), copy enclosed, demonstrated that histidine destabilized several proteins in terms of thermal transition, including RNase A, holo-α-lactalbumin, apo-α-lactalbumin, lysozyme and metmyoglobin. Therefore, the use of histidine in stabilizing IL-2 is not obvious.

Although Lee discloses the use of sucrose, histidine or glycerine to inhibit aggregation of antigen binding proteins, there is no hint that those substances, especially histidine, would be useful for stabilizing interleukins, especially the specific variant designated N88R. Use of sucrose, histidine, and/or glycine is not obvious for all proteins. As noted, proteins can be destabilized with certain amino acids, such as histidine and glycine. As mentioned above, cytochrome c was destabilized in the presence of histidine or arginine (Taneja and Ahmad, 1994). Several other proteins were destabilized in the presence of histidine or arginine, including RNase A, holo-α-lactalbumin, apo-α-lactalbumin, lysozyme and metmyoglobin (Rishi et al., 1998).

Although Nayar shows the use of histidine (with other substances) to stabilize FVIII there is no suggestion in that reference that histidine could be used (not as a destabilizer of proteins as taught above) as a stabilizer for interleukins, much less naturally occurring IL-2 (See enclosed data and declaration under 37 CFR 132) or the N88R mutein.

In view of the above amendments and distinctions it is submitted that this application now defines patentable subject matter and that the claims should be allowed. If the Examiner responsible for this application has any questions regarding the above amendments or enclosures that Examiner is invited to telephone the undersigned at any time.

PATENT
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Respectfully submitted,

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James A. Giblin
Attorney for Applicants
Reg. No. 25,772
Bayer Corporation
800 Dwight Way
P.O. Box 1986
Berkeley, CA 94701
(510) 705-7910